Clinical Pharmacology Review of Novel Erythropoiesis Stimulating Protein NESP

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The pharmacokinetics after intravenous or subcutaneous injection of NESP as single or multiple doses were studied in various clinical investigations in patients with chronic renal failure. These studies were: NESP 960224, NESP 970235, NESP 980194, and NESP 980212. The last cited study was conducted in a pediatric population. Trough samples were measured for up to 1 year in 5 studies, which are as follows: NESP 960245, NESP 960246, NESP 970200, NESP 980117, and NESP 980202. In studies NESP 960224 and NESP 970235, the pharmacokinetics of rh-EPO were compared to NESP after iv administration of single or multiple doses in patients with CRF. Study NESP 990134 was a pharmacokinetic bioequivalence study using single doses given sc in healthy volunteers of NESP in formulations containing either polysorbate and lacking HSA or those containing HSA.

1. Protocol NESP 960224, "A Comparison of the Pharmacokinetics of Novel Erythropoiesis Stimulating Protein (NESP) and Epoetin alfa in Patients with Chronic Renal Failure Receiving Dialysis." This was a single-center, open-label, randomized crossover of either rh-EPO (100 IU/kg) given IV or NESP (0.5 ug/kg) given IV and followed by a single-dose given sc. Patients (N = 11, 4 females, 7 males; mean age of 54.7) were enrolled in the study with chronic renal failure and receiving peritoneal dialysis whose hemoglobin was => 9 g/dl, with no previous rh-EPO therapy within 3 months. Various pharmacokinetic endpoints were determined including AUC, terminal t1/2, Vd and clearance. Following IV administration, clearance of NESP (1.6±0.28 ml/h/kg) was significantly lower than that of rhEPO (4.0±0.30 ml/h/kg) with p=0.0004; terminal t1/2 was also longer with NESP being 25.3±2.17 h and rh-EPO being 8.5±2.35 h with p=0.0008. No difference in Vd was observed. After sc injection the absorption of NESP was rate limiting on elimination; the terminal t1/2 was observed as 48.8±5.22 h with a bioavailability of 37%±3%. Serum concentrations of NESP and Epo were assessed using an ELISA assay.

Pharmacokinetic Endpoint	Epoetin alfa, IV, N=10, 100 IU/kg (0.5 ug/kg)	NESP, IV, N=11, 0.5 ug/kg	NESP, SC, N=6, 0.5 ug/kg
AUC0-infinity, ng-hr/ml	133± 0.7	311±9.84	108±11.0
Tmax, hr	---	---	54.1± 5.10
Cmax, ng/ml	13.5±0.676	13.2±0.622	0.94±0.0646
Vss, ml/kg	48.7±2.12	52.4±1.95	---
T1/2, hr	8.45 ±2.35	25.3±2.17	48.8±5.22

Table of pharmacokinetics in patients with chronic renal failure. Means and SE

2. Protocol NESP 970235, "A Randomized, Pharmacokinetic Study of Novel Erythropoiesis Stimulating Protein (NESP) and Recombinant Human Erythropoietin (r-HuEPO) Administered by Intravenous Bolus in Patients with End-Stage Renal Diseases (ESRD) Receiving Hemodialysis."

This study compares the IV pharmacokinetics of NESP to rh-EPO in hemodialysis patients with chronic renal failure given multiple injections of drug in a 3-arm multicenter, randomized, open-label design with a treatment duration of 52 weeks. In this multi-center study of the pharmacokinetics of NESP, patients (N = 47 enrolled; 32 were given NESP and N =15 were given rh-EPO) were enrolled who previously were given rh-EPO had chronic renal failure and were receiving dialysis. In these patients, treatment with rh-EPO had been given 3 times weekly for at least 2 months before the first dose of NESP. In those patients continuing to receive rh-EPO, their dosing regimen remained unchanged. NESP was administered to patients as either a once weekly or 3 times weekly regimen. In patients previously given rh-EPO, dosage was initiated on NESP given 3 times weekly at 1/5 their previous total weekly dose of EPO based on protein mass and 1/3 if EPO was given weekly. Doses were adjusted to maintain hemoglobin within the target range of 9.0 to 13.0 g/dl and within 1.0 g/dl below to 1.5 g/dl above the patient's baseline. Patients had hemoglobin levels of 9.0 to 12.5 g/dl. Steady-state pharmacokinetics was defined as the time at which a patient gained steady-state hemoglobin levels or between weeks 36 and 40, whichever occurred first.

Steady-state hemoglobin levels were defined as those being within the target range for hemoglobin for at least 4 weeks after 12 weeks with no change in study drug dosage. Additional study objectives were the safety of NESP in this patient population and the dosage needed to maintain a steady-state condition for hemoglobin. Only an interim analysis of the data up to June 29, 1999 is presently available was used in the pharmacokinetic study. Clearance, Vd-ss, terminal t1/2, AUC and dose normalized AUC were determined. Pharmacokinetic values were determined on day 1, at week 12 and at hemoglobin steady state (or between weeks 36 and 40, whichever came first). The pharmacokinetics of NESP and rhEPO were different with the terminal half-life being about 2 to 3 fold greater for NESP as compared to rhEPO; clearance was about 4 times slower. Upon repeated dosing for 36 weeks, the pharmacokinetics of NESP was as expected based on a linear model. When adjusted for dose, trough serum levels of NESP did not increase over time. No demographic covariates were identified with a significant impact on the pharmacokinetics of NESP in these patients.

3. Protocol NESP 980194, "A Pharmacokinetic Analysis of Chronic Subcutaneous NESP Therapy: A Supplemental Study to NESP 980140." This was a multi-center study in 16 patients (12 male and 4 female) and conducted in an open-label manner. The study was designed to characterize the pharmacokinetics of repeated sc dosing of NESP. The patient population evaluated was a subset of patients taken from protocol NESP 980140. Treatment duration was 8 weeks under study NESP 980194 with continuation of dosing under study NESP 980140 for an additional 44 weeks. These patients were being given once weekly sc doses. The goal of this study was to assess the pharmacokinetic profile of repeated sc administration in its relationship to dose and duration of therapy. Doses of NESP were titrated to individual patients with the goal of maintaining a target hemoglobin concentration between 9.0 to 13.0 g/dl and within 1.0 g/dl below to 1.5 g/dl above of the patient's baseline hemoglobin level. The pharmacokinetics of NESP was determined over 7 days during weeks 1 and 8. A dose-normalized AUC to the last collection time or extrapolated to infinity was calculated in addition to other endpoints (Tmax, Cl/F, Vd/F associated with terminal phase, terminal t1/2, mean residence time (MRT) to the last collected sample and MRT extrapolated to infinity. Dose dependency was determined by linear regression of pharmacokinetic endpoints for week 1 and week 8. The results are presented in the table immediately below.

Pharmacokinetic Endpoint	Week 1	Week 8
AUC, (ng-h/ml)/ng/kg	0.19±0.07	0.34±0.45
Tmax, h	31.9 (range 24 to 56)	31.8 (range 24 to 47)
Cl/F, ml-h/kg	6.0 ±2.32	4.5±2.73
T1/2, h	49.1±16.84	38.4±14.05
Vd/F, ml/kg	431.2±258.31	280.7±220.44
Cmax, ng/ml	0.9 ±0.52	1.7±2.08
MRT, h	95.5±22.52	65.4±13.97

Table of pharmacokinetic results of repeated sc dosing presented as mean and SD. Tmax is cited as the median value. T1/2 is the terminal t1/2. MRT and AUC are reported as extrapolated to infinity.

No evidence of a difference was found for the pharmacokinetics of NESP between weeks 1 and 8. Additionally, no evidence of dose or time dependency on the pharmacokinetics of NESP. Although trough levels for NESP gave no evidence of accumulation, a number of pharmacokinetic values suggest a change from week 1 to week 8. Namely, an increase in AUC was observed at week 8 coincident with a decrease in clearance and volume of distribution. Given the dispersion in the data, these values are not statistically significant and may have obscured an underlying change in disposition.

4. Protocol NESP 980212, "An Open-Label, Randomized, Crossover Study to Determine the Pharmacokinetics of Novel Erythropoiesis Stimulating Protein (NESP) in Pediatric Patients with Chronic Renal Failure (CRF) or End-Stage Renal Disease (ESRD)." Multicenter, open-label, randomized 2-period, crossover study of 2 doses of NESP (0.5 ug/kg) given IV on one occasion and later sc with a separation of 14 days. Patients (N = 8) were ages 1 to 16 years old with chronic renal failure undergoing dialysis and hemoglobin equal to or greater than 9 g/dl. No rhEPO was given within 7 days prior to the first dose of

NESP. Patients were ages 1 to 16 years of age with chronic renal failure; being on dialysis was not a precondition to enrollment. A baseline hemoglobin level of >9 g/dl and serum transferrin saturation > or equal to 20% were required for inclusion in the study. Various pharmacokinetic endpoints were determined including AUC extrapolated to infinity, Cmax, mean resident time extrapolated to infinity, clearance, and bioavailability. An estimate of the rate of absorption was also calculated. The table below summarizes the results and compares the pediatric data to adult pharmacokinetic values obtained in study NESP 960224.

Pharmacokinetic Endpoints	Adult (N=11)	Pediatric (N=6)
Cl, ml/h/kg	1.64 (range 1.3 to 2.0)	2.24 (range 1.6 to 3.5)
T1/2, h	25 (range 16.6 to 39.7)	20.5 (range 12 to 25)

Table of pharmacokinetic results for a single dose given IV. Mean and range are displayed.

Pharmacokinetic Endpoint	Adult (N=6)	Pediatric (N=4)
T1/2, h	48.4 (range 33.5 to 68.0)	32.5 (16 to 44)

Table of pharmacokinetic results for a single dose given SC. Mean and range are displayed.

After sc administration the absorption rate a limiting factor impacting the terminal elimination rate constant as measured by the terminal half-life. The t1/2 for IV administration was 20.5 h whereas after sc it was 32.5 h. Bioavailability was calculated to be 52%. NESP appears to be absorbed at a slightly faster rate in pediatric subjects although the overall pharmacokinetics is similar.

5. Protocol NESP 990134, "A Double-Blind, Randomized, Crossover Study to Compare the Pharmacokinetics and Safety of Subcutaneously Administered Single Doses of Two Formulations of Novel Erythropoiesis Stimulating Protein (NESP) in Healthy Subjects." This was a multi-center, double blind, randomized 2-period, crossover study of a single sc dose of either of 2 different formulations of NESP (1 ug/kg). Healthy volunteers (N = 28) were given both formulations with a 42-day washout period between injections. The 2 formulations were HSA-free NESP vs. NESP with HSA.

The pharmacokinetics of 2 formulations of NESP was compared after a single injection to healthy subjects. Injections were given sc as a 1.0 ug/kg dose with and without human serum albumin. The study was designed as a single-center, double-blind 2-period crossover study with randomized allocation of subjects to treatments. Twenty-eight subjects were enrolled in the study of which 15 were males and 13 females. The range of ages was 18 to 55 years of age with an average of 32.3 years. The primary endpoint was AUC as measured from time to the last quantifiable level. Secondary endpoints were Cmax, Tmax and AUC when extrapolated to infinity; other pharmacokinetics endpoints were also determined including terminal t1/2, clearance and volume of distribution. Additionally an assessment of safety was performed during the study that included an assessment of antibody formation. Results of the pharmacokinetic study are presented below.

Pharmacokinetic Endpoint	With HSA, N=28	Without HSA, N=28
AUC_{0-t}, ng-hr/ml	272 ± 7	278 ± 7
Cmax, ng/ml	3.5 ± 1	3.6 ± 1

Table of means and standard errors for untransformed pharmacokinetic endpoints in healthy subjects.

Pharmacokinetic Endpoint	HSA-free/HSA-with formulation (ratio 90% CI)
AUC0-t, ng-hr/ml, untransfomed	1.02 (0.96, 1.09)
AUC0-t, ng-hr/ml, transformed	1.02 (0.96, 1.09)
Cmax, ng/ml, untransformed	1.03 (0.96, 1.12)
Cmax, ng/ml, transformed	1.04 (0.96. 1.13)
AUC0-infinity, ng-hr/ml, untransformed	1.02 (0.95, 1.08)
AUC0-infinity, ng-hr/ml, transformed	1.02 (0.96, 1.08)

Table of pharmacokinetic endpoints presented as the ratio of means and 90% CI.

To determine the pharmacokinetic equivalence of the formulations with and without HSA, the ratio of the log transformed AUC and 90% confidence interval was computed and found to be 1.02 with 0.96 and 1.09 as the lower and upper limits. Thus the 2 formulations are considered to be bioequivalent. An ANOVA of the data failed to reveal a treatment-by-period interaction. Data for AUC and Cmax were normally distributed. No antibodies or clinically relevant toxicities were observed during the course of the study.

6. A Comparison of the Pharmacokinetics of Novel Erythropoiesis Stimulating Protein (NESP) and Epoetin alfa in Patients With Chronic Renal Failure Receiving Dialysis, protocol NESP 960224.

The pharmacokinetics of a single dose of NESP and Epoetin alfa was studies after IV administration in patients with chronic renal failure and receiving peritoneal dialysis. Additionally the pharmacokinetics of a sc injection of NESP was determined in this patient population. The study design was a single center, randomized, double-blind study incorporating a 2 period, 2 treatment crossover of NESP and Epoetin alfa. An IV dose of 0.5 ug of peptide mass/kg for NESP was compared to 100 IU/kg of Epoetin. Following the IV crossover study, patients were allowed to enter an open label single sc study of NESP at a dose of 0.5 ug of peptide mass/kg. The primary endpoint of the study was AUC, terminal elimination half-life and volume of distribution; a secondary endpoint was clearance. Safety was also assessed.

The pharmacokinetic results are summarized in the table below.

Pharmacokinetic endpoints	NESP	Epoetin alfa
AUC,		
Cl, ml/h/kg	1.6 ± 0.3	4. 0± 3
Vd, ml		
T1/2, h	25 ± 2.2	8.5 ± 2.3

Table 2. Means and standard errors for pharmacokinetic endpoints in patients with renal failure after IV administration.

The clearance of NESP was approximately 2.5 times lower after a single injection in patients with renal failure as compared to Epoetin alfa; concurrently, the terminal t1/2 was also approximately 3 times larger for NESP as compared to Epoetin alfa. The volumes of distribution were approximately the same. After sc injection absorption was rate limiting and the terminal t1/2 was determined to be 49 hours. Bioavailability was calculated to be 37% as an average value.

7. NESP 960245, A Dose-Finding and Dose-Scheduling Study of Novel Erythropoiesis Stimulating Protein (NESP) Administered by Intravenous Bolus in Patients With Chronic Renal Failure Receiving Hemodialysis. This study is ongoing and is reported as an interim analysis of data up to April 1999. This is a mutlicenter study to investigate the optimum dose and dose schedule of NESP for the treatment of anemia by IV bolus administration to patients with chronic renal failure receiving hemodialysis. Dosing was initially for a 4-week period and was extended to 16 weeks in patients attaining an optimal hemoglobin response during the first 4 weeks. Dosing could be continued in patients up to 52 weeks for maintenance. The optimal hemoglobin response was defined as a rate of rise of >or equal to 1g/dl and <3 g/dl. Only about 60 of 120 planned subjects have been enrolled in this study to date. Two different dosing regimens were investigated using a range of doses. One regimen was a once a week IV dosing at 0.075, 0.225, 0.45, 0.75, 1.5, and 4.5 ug/kg. The second dosing regimen was IV dosing 3 times weekly at doses of 0.025, 0.075, 0.15, 0.25, 0.5 and 1.5 ug/kg. For a given dose of NESP, the IV administration of once weekly or 3 times weekly yielded no evidence of trough accumulation. Trough was proportionate to dose and increased with a more frequent dosing regimen.

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